61. A composition comprising the polypeptide of claim 52 and a pharmaceutically acceptable carrier.

REMARKS

Applicants respectfully remind the PTO that the firm of Finnegan, Henderson, Farabow, Garrett, & Dunner, L.L.P. is now handling this application as per the Power of Attorney filed on October 31, 1996. The new Attorney Docket No. is 02356.0074-00000.

The title has been amended to correct a typographical error.

Support for this amendment can be found throughout the specification, for example, at page 31, line 3 through page 32, line 9, and original claims 1-38. Accordingly, this amendment adds no new matter and entry of this amendment is respectfully requested.

Applicants have canceled claims 18, 19, and 37-39 and added claims 40-61. Claims 40-45 recite a purified polypeptide having the amino acid sequence of at least one of the polypeptides selected from the group consisting of UreE, UreF, UreG, UreH, and UreI as shown in Figure 4 (SEQ. ID NOS: 4-7 and 3, respectively), or a fragment thereof. Claims 46-52 recite a purified polypeptide having an amino acid sequence expressed by a gene selected from the group consisting of ureE, ureF, ureG, ureH, and ureI (SEQ ID NO:1) of H. pylori, or a mutant thereof. Although each of these genes is contained within SEQ ID NO:1, each is a distinct gene. Claims 53-55 are directed to antibodies, that bind to the purified polypeptides of the claimed invention. The compositions of claims 56-58 comprise the antibodies of claim 53-55 and a pharmaceutically

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& DUNNER, L.L.P.
1300 I STREET, N. W.
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acceptable carrier. The compositions of claims 59-61 comprise a polypeptide of the claimed invention and a pharmaceutically acceptable carrier.

Applicants' amended claims render the subject matter for which protection is sought more clear and concise. For example, the amended claims now recite a single member of the Markush group of original claim 18. Each member of the original Markush group was individually recited in claim 18. Accordingly, no new matter is added and no new search is required by this amendment.

Applicants have included the term "mutant" in claims 46-51. This term is fully supported by the specification as filed. See, for example, page 13, lines 18-26, which identify variants of the nucleotide sequences corresponding to ureE, ureF, ureG, ureH, and ureI as part of applicants' invention and defines the resulting expressed polypeptides as those having a functional homology with the UreE, UreF, UreG, UreH, and UreI polypeptides expressed by *H.pylori* or those which suppress the functional properties of the UreE, UreF, UreG, UreH, and UreI polypeptides expressed by *H.pylori*. Other modifications at the nucleotide level giving rise to mutant urease polypeptides are described with specificity at page 15, lines 6-18. Modified or mutant polypeptides themselves are specifically described at page 18, lines 17-27; page 20, lines 16-35; page 21, lines 20-30. Construction of mutants of this invention is described in Figure 12 and at pages 31-32.

Applicants acknowledge that the present application contains claims to non-elected subject matter. Applicants will cancel those claims from this application upon an indication that the elected claims are allowable.

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The specification is objected to and claims 37 and 38 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that the specification lacks an enabling disclosure because it purportedly does not teach how to obtain the antibodies of claim 37 and the compositions of claim 38.

Specifically, the Examiner alleges (1) that it is unclear whether changes or modifications that occur in the gene will affect the antigenic determinants in order to obtain a composition to treat infection caused by *H. pylori*; (2) that the *H. pylori* urease antigenic determinants or epitopes, which can be used to obtain the antibodies and composition of the claimed invention, have not been disclosed; and (3) that it is unclear how to obtain the fragments of the polypeptides. The Examiner concludes that one skilled in the art would be required to practice undue experimentation in order to make and/or use the claimed invention.

Applicants respectfully traverse the rejection.

The Federal Circuit has stated the test for the enablement requirement of 35 U.S.C. § 112, first paragraph:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed.Cir. 1986), cert. denied, 480 U.S. 987 (1987). Applicants' specification provides sufficient guidance to teach one having reasonable skill in the art how to make and use the claimed invention.

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Applicants have canceled claims 18, 19, and 37-39. Newly added claims 40-45 recite a purified polypeptide having the amino acid sequence of at least one of the polypeptides selected from the group consisting of UreE, UreF, UreG, UreH, and UreI as shown in Figure 4 (SEQ. ID NOS: 4-7 and 3, respectively), or a fragment thereof. Newly added claims 46-51 recite a purified polypeptide having an amino acid sequence expressed by a gene selected from the group consisting of ureE, ureF, ureG, ureH, and ureI (SEQ ID NO:1) of H. pylori, or a mutant thereof. Although each of these genes is contained within SEQ ID NO:1, each is a distinct gene. In addition, the newly added claims 53-55 are directed to antibodies, that bind to the purified polypeptides of the claimed invention. The compositions of claims 56-58 comprise the antibodies of claim 53-55 and a pharmaceutically acceptable carrier. The compositions of claims 59-61 comprise a polypeptide of the claimed invention and a pharmaceutically acceptable carrier. It is believed that these amendments obviate the rejections under 35 U.S.C. § 112, first paragraph.

Applicants respectfully point out that the "fragments" of the purified polypeptides of claim 40 are enabled by the specification. For example, the passage at page 14, line 27 through page 4, line 9 specifically addresses the fragments of the claimed invention. In addition, at page 15, lines 1-5, applicants provide a simple assay to determine whether a polypeptide fragment is within the scope of the invention:

> This functional homology can be detected by implementing the following test: 10^9 bacteria are resuspended in 1 ml of urea-indole medium and incubated at 37°C. The hydrolysis of the urea leads to the release of ammonia which, by raising the pH, leads to a colour change from orange to fuchsia.

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(Specification at page 15, lines 1-5). Therefore, applicants respectfully submit that it would require only routine experimentation by one having ordinary skill in the art to determine what fragments are useful in the claimed invention.

Similarly, the specification enables making and using the polypeptides expressed by mutants as set forth in claims 46-51. For example, at pages 35-39 of the specification, applicants teach that cloned DNA of H. pylori was subjected to mutagenesis, wherein insertional mutations and deletions were observed. Out of 24 insertions selected for analysis, 10 derived plasmids lost the ability to hydrolyze urea. (Specification, page 35, last paragraph.) Based on these results, Applicants were able to assess the necessity of the accessory genes in the expression of a functional urease.

Moreover, the assays for identifying, localizing, and analyzing the mutants of the claimed invention are set forth at pages 35-36 of the specification. Applicants teach transforming host cells with the resulting mutants of the cloned DNA in plasmids. The transformed host cells were evaluated under nitrogen-limiting conditions to determine the effects of the mutagenesis and digestion of cloned DNA on urease activity. (Specification, page 36, first full paragraph.) Table 2 provides the results of this study. Accordingly, one having skill in the art would readily appreciate how to make and use the claimed invention.

Regarding the method of obtaining the antibodies of the claimed invention, applicants respectfully submit that the specification provides ample support to teach one of skill in the art to make and use the antibodies of the claimed invention. For example, at page 18, last paragraph, applicants teach that:

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> The polypeptides of the invention and in particular the polypeptides whose sequence is given above can be used for the production of monoclonal or polyclonal antibodies, or for the detection of antibodies in a biological sample infected by H. pylori.

Moreover, at page 19, the specification describes the methods of obtaining the antibodies of the claimed invention:

> Monoclonal antibodies can be prepared by the hybridoma procedure or by known procedures for the preparation of human antibodies.
> These antibodies can also be prepared according to the procedure described by Marks et al. (J. Mol. Biol. 1991 222, 581-597).

With their Amendment After Final, submitted January 21, 1997, Applicants provided three articles that describe known methods of making polyclonal and monoclonal antibodies at the time the claimed invention was made.

Thurlow and McKenzie, "Monoclonal Antibodies in Clinical Medicine - A Review", Australian and New Zealand Journal of Medicine, 13(1):91-100 (Feb. 1983), for example, provide an overview of how to make monoclonal antibodies in 1983, well before the effective filing date of the instant application. At pages 91-92, the authors provide the steps of immunizing, fusing, screening, and cloning in order to produce monoclonal antibodies. In addition, at page 93 of Thurlow and McKenzie, the authors describe the clinical interest in and advantages of monoclonal antibodies. Therefore, one having skill in the art would appreciate how to both make and use the claimed monoclonal antibodies.

In addition, Berzofsky et al., "Antigen-Antibody Interactions and Monoclonal Antibodies", Fundamental Immunology, Second Edition, Raven Press Ltd.: New York (1989), pp. 315-351 further describe antibodies, their production, and activity. At page 316, Berzofsky et

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al. teach that ". . . antibodies can be raised, by design of the investigator, with specificity for almost any substance known. In each case, one can find antibodies with affinities as high as and specificities as great as those of enzymes for their substrates and receptors for their hormones." (Emphasis supplied.) At pages 347-350, the authors also describe the production of monoclonal antibodies. Thus, raising antibodies against any antigen was well-known in the art before applicants' filing date, and the Berzofsky et al. publication further supports a finding that one having skill in the art would have been able to produce the antibodies of the claimed invention.

Finally, Hurn and Chantler, Methods in Enz., 70: 104-142 (1980) discuss methods for producing and purifying polyclonal and monoclonal antibodies, the preparation of columns where immunological complexes are formed, and the labeling of purified antibodies to ultimately detect immunological complexes.

In view of these three references, it is clear that methods for obtaining the antibodies of the claimed invention were known in the art at the time the claimed invention was made. An applicant need not teach and preferably omits descriptions of well known techniques from a patent specification. Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir. 1987). The present specification conforms to that preference.

The PTO has the burden of establishing a *prima facie* case of lack of enablement. In re Marzocchi, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Furthermore, applicants' specification disclosing how to make and use the claimed invention must be taken as in compliance with § 112, first paragraph, unless there is a reason to doubt the objective truth of the disclosure. In re Brana, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1437, 1442 (Fed. Cir. 1995). No reasons sufficient to

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cast doubt on Applicants' teachings have been provided. One having ordinary skill in the art would be capable of practicing the claimed invention, and withdrawal of the enablement rejection is respectfully requested.

Claims 18, 19, 37, and 38 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

Applicants have canceled claims 18, 19, 37, and 38 and replaced them with claims 40-61. Applicants believe that the newly added claims render the instant rejection moot. Accordingly, withdrawal of the rejection is respectfully requested.

Applicants acknowledge the withdrawal of the §§ 102/103 rejection in the Advisory Action dated March 20, 1997.

In view of the foregoing, applicants respectfully submit that this application is now in condition for allowance. Applicants request that this Amendment under 37 C.F.R. § 1.129(a) be entered by the Examiner. Moreover, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims are earnestly solicited.

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FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
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The Examiner is invited to call the undersigned to discuss any outstanding issues in order to expedite prosecution.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Leslie A McDonell
Leslie A. McDonell
Registration No. 34,872

Dated: May 5, 1997

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